Nasal versus bronchial and nasal response to oral aspirin challenge: Clinical and biochemical differences between patients with aspirin-induced asthma/rhinitis

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Background: Aspirin-induced asthma/rhinitis (AIAR) is characterized by the altered metabolism of leukotrienes and proinflammatory prostaglandins. The basal and postchallenge levels of eicosanoids might reflect the clinical and biochemical characteristics of patients with distinct types of hypersensitive responses to aspirin.

Objective: We compared clinical and eicosanoid profiles of patients with AIAR showing both bronchial and nasal versus isolated nasal responses to aspirin challenge.

Methods: Twenty-three patients with AIAR underwent the single-blind, oral, placebo-controlled aspirin challenge. The bronchial response (BR) was evidenced by dyspnea and spirometry, whereas the nasal response (NR) was evidenced by nasal symptoms and acoustic rhinometry and/or rhinomanometry. Urinary leukotriene E_4 ($uLTE_4$), serum and urinary stable prostaglandin D_2 metabolite, and 9α,11β-prostaglandin F_2 (9α,11β-PGF_2), were determined at baseline and after the aspirin challenge.

Results: Fifteen subjects showed BR and NR (BNR), whereas 8 showed NR only. Basal $uLTE_4$ in the BNR group was significantly higher than in the NR group. After aspirin challenge, it increased significantly in both groups. Serum 9α,11β-PGF_2 increased after aspirin challenge in the BNR group only. The patients with BNR had more severe AIAR.

Conclusions: BNR to aspirin in AIAR indicates a more advanced disease and more profound underlying eicosanoid metabolism disturbances. (J Allergy Clin Immunol 2003;112:995-1001.)

Key words: *Aspirin-induced asthma/rhinitis, aspirin challenge, leukotriene E_4, prostaglandin D_2, 9α,11β-prostaglandin F_2*

Abbreviations used

AIAR:	Aspirin-induced asthma/rhinitis
ASA:	Aspirin
LTE_4:	Leukotriene E_4
PGD_2:	Prostaglandin D_2
9α,11β-F_2:	9α,11β-prostaglandin F_2
GC-NICI-MS:	Gas chromatography–negative-ion chemical ionization–mass spectrometry

Up to 10% of asthmatic patients are intolerant to aspirin and other nonsteroidal anti-inflammatory drugs, reacting with bronchospastic and/or naso-ocular symptoms when exposed to the offending drugs. This syndrome is referred to as the aspirin-induced asthma/rhinitis, AIAR.[1-4] At the biochemical level, AIAR is characterized by a chronic leukotriene overproduction and an increased urinary excretion of a stable prostaglandin D_2 (PGD_2) metabolite, 9α,11β-PGF_2, observed in a proportion of patients.[1-6] In AIAR, chronic degranulation of mast cells and eosinophils is probably ongoing in the upper and lower airways. Eicosanoids originating from these cells play an important role in the inflammation of the respiratory mucosa, enhancing vascular permeability, plasma protein exudation, and inducing bronchospasm and nasal blockage.

The AIAR syndrome develops in line with a characteristic sequence of symptoms, similar in Europe and the United States.[7,8] Rhinorrhea and nasal congestion are usually the first symptoms of AIAR, and patients often report a typical virus-like infection before the onset of rhinitis. It becomes persistent, perennial, and associated with chronic sinusitis and nasal polyposis. Asthma and sensitivity to aspirin become manifest on average 2 to 3 years after the onset of rhinitis.

The accurate diagnosis of AIAR is based on oral, inhaled, nasal, or intravenous placebo-controlled provocation tests with increasing doses of aspirin.[1-3] After oral aspirin challenges, Pleskow et al[9] showed a spectrum of respiratory responses. Aspirin intolerance remains underdiagnosed worldwide.[3] This may be attributable to the fact that the gold standards in diagnosing aspirin-induced asthma/rhinitis are the oral and inhaled aspirin challenges, frequently focusing on bronchial symptoms, as

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easily confirmed by objective and standardized methods. Nasal provocation is believed to be less sensitive and the nasal response more variable.[1-3]

Some authors suggest that even 40% of patients with nasal polyposis show aspirin hypersensitivity.[3] It is quite likely that patients who do not have bronchospasm induced by aspirin and other nonsteroidal, anti-inflammatory drugs are not considered to be aspirin-sensitive.[9] Furthermore, it was established that the inclusion of extrabronchial, mainly nasal symptoms, into the criteria of aspirin challenge positivity significantly enhanced the diagnostic value of the challenge procedure.[10]

The study aimed to compare the clinical and biochemical characteristics of patients with AIAR showing different responses to single-blind, oral, placebo-controlled aspirin provocation challenges.

METHODS

Study subjects

Twenty-three patients with asthma and chronic rhinosinusitis (8 men, 15 women; mean age, 43 years) participated in the study. All patients gave a history of prior reaction to aspirin and/or other nonsteroidal, anti-inflammatory drugs. The doses of nasal, bronchial, and oral corticosteroids remained unchanged during the course of the study. The antihistamines were withheld 10 days before the aspirin challenge. Theophylline was discontinued for 48 hours, the long-acting β_2-agonists for 12 hours, and the short-acting β_2-agonists for 8 hours before the aspirin challenge. Two of 23 patients were treated with leukotriene receptor antagonists; these patients were asked to discontinue the therapy at least 3 weeks before the aspirin challenge. Informed consent approved by the local bioethics committee was signed after the nature of the procedures was explained.

The aspirin challenge

Single-blind, 2-day, placebo-controlled, aspirin oral challenges were conducted in all patients, based on the slightly modified method of Nizankowska et al.[10] On the first day, placebo was administered twice every 2 hours. On the second day, patients received every 2 hours 4 incrementally increasing aspirin doses (27, 44, 117, and 312 mg; the cumulative aspirin dose equaled 500 mg).

The evidence of clinical symptoms, such as dyspnea, rhinorrhea, nasal congestion, sneezing, ocular injection, or skin flushing, was assessed on an hourly basis.

At baseline and every 30 minutes until 2 hours after the last dose of placebo or aspirin administration, serial spirometry measurements of respiratory function were taken (abcPneumo 2000RS, abcMED, Krakow, Poland). Acoustic rhinometry (Rhinoscan, Rhinometrics A/S, Lynge, Denmark) and rhinomanometry (Homothrhino 2002, Homoth Medizinelektronik, Hamburg, Germany) readings were taken at the same time points as the spirometric measurements. The parameter evaluated by acoustic rhinometry was the total nasal volume at 12 cm (the sum of nasal volume values recorded from each nostril to 12 cm distally).[11] Left and right nasal flow inspiratory and expiratory volumes were assessed by the active anterior rhinomanometry. Rhinomanometry was not carried out in subjects with nasal inspiratory flow <250 mL/s at baseline.

The positive bronchial reaction (BR) to aspirin was defined as the appearance of dyspnea and at least 20% decrease in FEV_1 compared with baseline FEV_1. In any such case, the aspirin challenge was terminated and the nebulized β_2-agonist was used to treat the aspirin-induced asthmatic reaction until the symptoms resolved and FEV_1 returned to its prechallenge values.

The positive nasal reaction (NR) to aspirin challenge was defined as the appearance of nasal symptoms such as rhinorrhea, nasal congestion, sneezing, and 25% decrease of total nasal flow value at 12 cm, as compared with baseline measured by acoustic rhinometry, and/or 40% unilateral drop of inspiratory nasal flow, as compared with baseline value assessed by rhinomanometry. Topical oxymetazoline was used to treat nasal obstruction after aspirin challenge.

Laboratory assessment

The urine for leukotriene E_4 (LTE_4) excretion assessment was collected at baseline and after 1.5, 3, and finally at 4.5 hours after positive BR to aspirin challenge or after the last dose of aspirin in the case of nasal reaction only. The stable PGD_2 metabolite, 9α,11β-PGF_2, was evaluated in serum at baseline and 5, 30, 60, and 120 minutes after positive BR to aspirin challenge or after the last dose of aspirin in the case of nasal reaction only. The measurements of 9α,11β-PGF_2 excretion in urine were taken at the same time intervals as the ones for LTE_4. Baseline urine samples were collected after a 2-hour accumulation in the bladder. LTE_4 enzyme immunoassay kits were obtained from Cayman Chemicals (Ann Arbor, Mich). The LTE_4 was assessed as described by Kumlin et al.[12] The 9α,11β-PGF_2 was evaluated both in serum and urine by gas chromatography–negative-ion chemical ionization–mass spectrometry (GC-NICI-MS, Hewlett Packard, Palo Alto, Calif), with the use of the electron impact method, with the pentadeuterated $PGF_2\alpha$ used as an internal standard according to Obata et al.[13]

Clinical data analysis

The following clinical data were specifically recorded: age, sex, nasal polyposis, number of polipectomies, duration of asthma, duration of aspirin hypersensitivity, rhinitis, and nasal polyposis. Information on asthma and rhinosinusitis therapy was also collected, and all patients were interviewed on the number of hospitalizations and emergency interventions for asthma exacerbation.

The following laboratory measurements were taken: absolute eosinophil blood count (cell number/mm^3), total serum IgE (IU/mL), and eosinophil percentage in the nasal cytology (percent of total cell count). Spiral computed tomography (CT, ElScint Flash, Haifa, Israel) point score of sinus involvement was assessed,[14] and skin tests with 14 common aeroallergens were carried out (Soluprick, ALK, Hørsholm, Denmark).

Statistical analysis

Statistical evaluation was carried out with a PC and STATISTIC software (Statsoft Inc, Tulsa, Okla). Summary statistics were expressed as mean and standard deviation. One-way and multiway analysis of variance was used for comparing the respective groups and post hoc Tukey procedure for running multiple comparisons. Logarithmic transformation was used as variance stabilizing transformation when required. The Mann-Whitney *U* test was used for comparing clinical/treatment data and the results of examinations in the respective groups. The Fisher exact test was used for assessing significance in the 4-fold tables. A value of $P \leq .05$ was considered statistically significant.

RESULTS

In 15 of 23 patients, the aspirin challenge induced both bronchial and nasal response (BNR), whereas in 8 of 23 patients it provoked the NR only. All patients from the BNR group and none of the NR group had dyspnea after the aspirin challenge. All patients both from the BNR and the NR groups showed such nasal symptoms as watery rhinorrhea, nasal congestion, and sneezing of varying intensity. The ocular symptoms, for example, ocular injection,

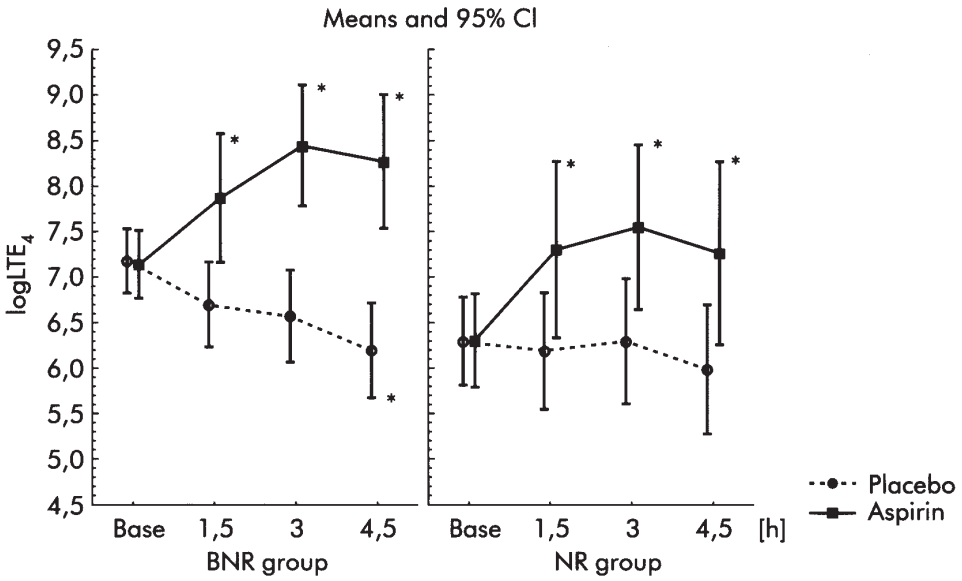

FIG 1. Mean baseline $uLTE_4$ (expressed as log $uLTE_4$ change in time) excretion in BNR and NR groups. *Statistically significant compared with baseline (also see Table I).

TABLE I. Urinary leukotriene E_4 and 9α,11β-prostaglandin F_2 levels at baseline and after placebo or aspirin

	Baseline	1.5 h	3.0 h	4.5 h
LTE_4 (pg/mg creat)				
BNR				
PL	1593 ± 901	1091 ± 887	1038 ± 901	707 ± 529‡
ASA	1490 ± 863	3935 ± 2649†	6813 ± 4878‡	5768 ± 3937†
NR				
PL	593 ± 214	722 ± 679	841 ± 868	579 ± 582
ASA	734 ± 670	3143 ± 4039†	3235 ± 2729‡	2899 ± 2481*
9α,11β-PGF_2 (ng/mL creat)				
BNR				
PL	0.8	0.8 ± 0.5	0.8 ± 0.4	0.9 ± 0.7
ASA	0.60 ± 0.2	0.6 ± 0.4	0.6 ± 0.2	0.6 ± 0.3
NR				
PL	0.5 ± 0.2	0.7 ± 0.5	0.7 ± 0.4	0.8 ± 0.7
ASA	0.7 ± 0.3	1.0 ± 0.7	0.8 ± 0.5	0.6 ± 0.3

Values are expressed as mean ± SD.
BNR, Bronchial and nasal response; *NR*, nasal response; *ASA*, aspirin; *PL*, placebo.
*$P < .05$; †$P < .01$; ‡$P < .001$ as compared with baseline.

accompanied nasal symptoms in every case. The flushing of the face, the only skin symptom encountered in both groups, was observed in 2 of 15 patients with BNR and in 2 of 8 patients with NR to aspirin. None of the patients had urticaria, angioedema, laryngospasm, or other symptoms after the aspirin challenge. The mean decrease in FEV_1 in the BNR group was 26.7%, whereas in the NR group it was 7.2%. The mean total nasal volumes and baseline and after aspirin in the BNR group were 53 ± 18.1 cm^3 and 25 ± 13.5 cm^3, whereas in the NR group it was 77.4 ± 22.8 cm^3 and 36 ± 14.6 cm^3, respectively. The mean decrease in total nasal volume after aspirin challenge in the BNR group was 52%, whereas in the NR group it was 50%. The mean inspiratory nasal flow at baseline and after aspirin was 318 ± 50 mL/s and 92 ± 44 mL/s in the BNR group, whereas in the NR group it was 379 ± 63 mL/s and 149 ± 47 mL/s, respectively. The mean decrease in inspiratory nasal flow after aspirin challenge in the BNR group was 72%, whereas in the NR group it was 58%. The mean aspirin PD_{20} in the BNR group was 103.7 ± 93 mg. All nasal reactors had nasal symptoms only after the last dose of aspirin (312 mg; cumulative dose, 500 mg). Placebo challenge was negative in all cases. The mean baseline urinary LTE_4 excretion before both placebo and aspirin challenge was 3- and 2-fold higher in the BNR group compared with the NR group ($P < .01$ and $P = .01$, respectively) (Table I). No significant day-to-day variations of baseline $uLTE_4$ measurements between placebo or aspirin challenge were found.

Aspirin oral challenge induced a further 4-fold increase of the mean $uLTE_4$, as compared with baseline, both in the BRN and NR groups (Table I). The rise of this metabolite was more accentuated in the BNR group. The absolute mean values of $uLTE_4$ at 1.5, 3, and 4.5 hours after aspirin

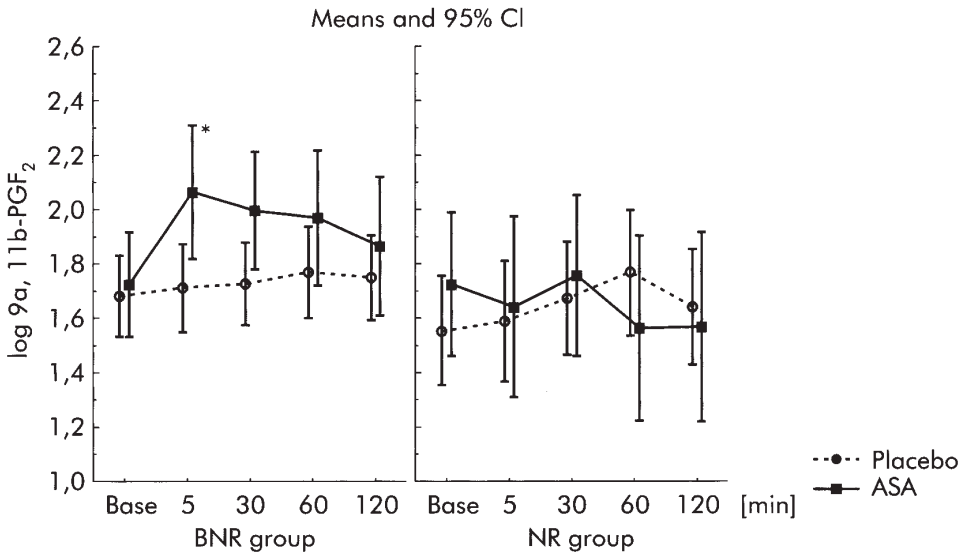

FIG 2. Mean baseline serum levels of 9α,11β-PGF_2 (expressed as log s9α,11β-PGF_2 change in time) in BNR and the NR groups. *Statistically significant compared with baseline (also see Table II).

TABLE II. Serum 9α,11β-prostaglandin F_2 levels at baseline and after placebo or aspirin

9α,11β-PGF_2 (pg/mL)	Baseline	5 min	30 min	60 min	120 min
BNR					
PL	6.0 ± 2.7	6.2 ± 3.1	6.3 ± 3.0	6.6 ± 3.4	6.3 ± 2.8
ASA	6.7 ± 5.4	10.2 ± 8.2*	9.2 ± 7.4	10.1 ± 11	9.3 ± 11
NR					
PL	4.8 ± 0.6	5.0 ± 1.6	5.4 ± 1.1	6.2 ± 2.4	5.6 ± 2.9
ASA	5.7 ± 1.3	5.2 ± 0.8	5.9 ± 1.1	5.0 ± 1.3	5.0 ± 1.3

Values are expressed as mean ± SD.
BNR, Bronchial and nasal response; *NR*, nasal response; *ASA*, aspirin; *PL*, placebo.
*Levels significantly different from baseline ($P < .05$).

challenge were higher in the BNR group, reaching its peak at the 3rd hour (Table I). There was a tendency to mean $uLTE_4$ decrease during the placebo day, which reached statistical significance at 4.5 hours in the BNR group. The $uLTE_4$ changes during the placebo and aspirin challenges in the respective groups are shown in Fig 1.

The mean baseline urinary 9α,11β-PGF_2 levels before both placebo and aspirin challenges were not significantly different between the BNR and NR groups (Table I). There was no significant increase of u9α,11β-PGF_2 after the aspirin challenge in any of the groups (Table I).

The mean baseline serum levels of 9α,11β-PGF_2 before both placebo and aspirin challenges showed no significant difference between the 2 groups (Table II). The aspirin challenge induced a significant, mean 1.5-fold increase of s9α,11β-PGF_2 only in the BNR group (Table II). The increase of this metabolite occurred immediately after the positive response and continued for 120 minutes. The changes of 9α,11β-PGF_2 levels in serum during placebo and aspirin challenge in the BNR and NR group are shown in Fig 2.

The clinical data are summarized in Table III. The statistical analysis indicated that patients with BNR appeared to have a more severe form of AIAR. They showed a tendency to longer mean duration of both asthma and nasal polyposis compared with the NR group. Furthermore, patients with BNR required significantly more emergency interventions.

Patients with BNR were usually subjected to slightly more aggressive oral, bronchial, and nasal steroid treatment, as compared with the patients with NR, although the differences between the respective regimens did not reach statistical significance. The mean overall duration of bronchial corticotherapy was significantly higher in the BNR group.

The mean baseline point CT score of sinus involvement was significantly greater in the BNR group compared with the NR group. The type of the involved sinus did not statistically correlate with either the BNR or the NR.

On the other hand, the patients with NR showed more frequently positive reactions to common aeroallergens.

TABLE III. Clinical profile of patients with bronchial and nasal and isolated nasal response

	BNR group, n = 15	NR group, n = 8	*P* value
Clinical data			
Age (y)	45 ± 14.3	38.4 ± 8.7	NS
Sex (F/M ratio)	11/4	4/4	NS
Aspirin intolerance onset (y)	6.9 ± 6.9	3.3 ± 3.3	NS
Asthma duration (y)	6.8 ± 6.2	2.9 ± 3.5	.08
Rhinitis duration (y)	13 ± 9	7.7 ± 6.2	NS
Patients with nasal polyposis	13	4	NS
Nasal polyposis duration (y)	5.1 ± 4.9	1.8 ± 3.5	.07
Polipectomies (n)	10	3	NS
Patients with (+) skin tests to allergens	2	5	.03
Hospitalizations due to asthma	1.5 ± 1.6	0.4 ± 0.5	NS
Emergency interventions	8	0	.02
Treatment			
Patients taking the oral corticosteroids	7	1	NS
Overall therapy duration (y)	1.2 ± 2.4	1 ± 2.8	NS
Dose before aspirin challenge (mg)*	0.87 ± 2.4	0.5 ± 1.4	NS
Patients taking inhaled corticosteroids	14	5	NS
Overall therapy duration (y)	5.1 ± 4.5	1.8 ± 2	.02
Dose before aspirin challenge (μg)†	877 ± 582	600 ± 565.7	NS
Patients taking nasal corticosteroids	13	5	NS
Overall therapy duration (y)	2.9 ± 4	1 ± 1	NS
Dose before aspirin challenge (μg)‡	33.7 ± 50	81.3 ± 99.8	NS
Results of exams			
Baseline FEV1 (% of predicted value)	87.2 ± 11.5	84.7 ± 13.1	NS
Abs eosinophil blood count (per mm^3)	587.5 ± 406.5	561.6 ± 390.3	NS
Eosinophil % in nasal cytology	13.6 ± 14	9.8 ± 19.7	NS
Serum IgE (UI/mL)	88.4 ± 93.5	97 ± 108.7	NS
Point score of sinus involvement in CT	28.3 ± 6.4	18.6 ± 13.6	.04

Values are expressed as mean ± SD.
BNR, Bronchial and nasal response; *NR*, nasal response.
*Daily dose recounted for methylprednisolone.
†Daily dose recounted for budesonide.
‡Daily dose of nasal budesonide.

DISCUSSION

In our study, 15 of 23 patients with AIAR showed typical bronchial and nasal responses to aspirin challenge, whereas 8 had isolated nasal response, confirmed by acoustic rhinometry and/or active anterior rhinometry. Such isolated nasal response was first described in detail by Lumry et al.[15] The relatively high proportion of patients with isolated NR observed by other authors[3,8,9,10,15,16] and in our own study gives reasonable grounds to believe that disregarding the nasal symptoms during the aspirin challenges may easily lead to misdiagnosis, as the symptoms from the upper respiratory tract are most likely to be the only manifestation of aspirin hypersensitivity in the early stage of AIAR.

The hypothesis that aspirin hypersensitivity is mediated by a deviation of the arachidonic acid metabolic pathway toward excessive leukotriene production and relative PGE_2 depletion, which then results in the clinical features of AIAR, is well recognized.[1-4] An increased baseline and postchallenge urinary LTE_4 excretion in AIAR was also observed in our study, corroborating the results reported by other authors.[12,13]

In our study, the mean baseline absolute values of LTE_4 were higher in the BNR group. The levels of this metabolite after aspirin challenge were also higher in this group, although the patients received smaller doses of aspirin as compared with the patients with NR only. The baseline LTE_4 value was correlated with a specific type of postchallenge reaction to aspirin and the clinical profile of AIAR.[16-18] Very much in line with our findings, Daffern et al[16] reported that the severity of the respiratory reactions varying from naso-ocular to bronchial ones during the oral aspirin challenges was associated with the degree of elevation of baseline LTE_4 excretion in urine. Notwithstanding, Oosaki et al[17] failed to find an association between the high value of baseline urinary LTE_4 and the type of asthma, severity of disease, oral prednisolone treatment, sex, or age. Kanny at al[18] reported that no significant differences between the baseline and postprovocation urinary LTE_4 levels were found in patients with a history of aspirin hypersensitivity and the healthy control subjects. Nevertheless, in Kanny's study, the heterogeneous groups of patients with aspirin hypersensitivity were studied (urticaria/facial edema, nasal polyposis, asthma and nasal polyposis, anaphylactoid shock), and a different aspirin challenge procedure was followed.

One might reasonably pose a question of whether the observed differences implicate AIAR heterogeneity or

are perhaps indicative of an evolutionary phase of the disease. Hence, we compared the clinical profile of patients with BNR and NR only, with a view to gaining a deeper insight into this issue.

The results indicated that the patients with BNR tended to be older and were characterized by longer duration of aspirin hypersensitivity, asthma, rhinitis and nasal polyposis, and more severe manifestations of the disease, and they had been subjected to a more intensive antiasthmatic therapy. The higher frequency of positive skin test results to common aeroallergens in the patients with NR to aspirin might perhaps be attributable to the fact that those patients were younger than the ones with BNR. Interestingly, the results of the large epidemiologic study on AIAR in Europe disclosed that rhinitis and asthma appeared significantly earlier in patients with positive skin test results as compared with those with the negative results.[7] The tendency to a more severe manifestation of asthma might possibly account for the elevated baseline morning urinary LTE_4 excretion values in the BNR group.

The other source of an excessive urinary LTE_4 excretion in patients with AIAR might be the more severe chronic rhinosinusitis associated with nasal polyps, a key attribute of aspirin hypersensitivity.[1-3] In fact, we did find more extensive nasal polyposis in the BNR group, which was documented by a significantly higher CT sinus involvement score and a tendency to a longer duration of the sinus disease. This might suggest that in our study, patients with the bronchial/nasal response had AIAR in its advanced phase and the ones with isolated nasal responses had AIAR in its earlier phase.

Another viable possibility of the milder response to aspirin challenge might be a clinical remission after pharmacotherapy in some NR patients. The notion that baseline LTE_4 might be correlated to the underlying bronchial and nasal reactivity after aspirin challenge is much in line with the observations that aspirin-induced reactions vary from time to time within an individual.[3,9] Some patients with the background of violent bronchospastic response to aspirin challenge may react with isolated nasal symptoms when rechallenged within the period of well-controlled asthma.[9] Notably, in one of the patients with nasal response who participated in the current study, the bronchial symptoms were elicited by the oral and inhaled aspirin challenge conducted in the past. Finally, the isolated nasal response to aspirin could be the only manifestation of aspirin hypersensitivity in a subset of patients with pure aspirin-sensitive rhinitis.[9,15]

The mean baseline urinary LTE_4 values were found not to differ between the placebo and aspirin day. However, the majority of patients, mainly from the BNR group, on the placebo day had their baseline urinary LTE_4 values higher than in the consecutive samples. There are many factors implicated in the variability of urinary LTE_4 excretion. We checked the corresponding morning creatinine values and found them to be slightly elevated (data not shown), although not proportionally so with respect to the urinary LTE_4 excretion in all cases. This might be due to the increased urine density after the night. The daily urinary LTE_4 excretion values in asthmatic patients and healthy control subjects were found to be variable.[13,19] Circadian rhythmicity of urinary LTE_4 excretion with the morning peaks in healthy control subjects and patients with nocturnal asthma was recently described.[19]

The role of proinflammatory and bronchospastic eicosanoid metabolites originating from arachidonic acid through the cyclooxygenase biochemical pathway in AIAR still requires further in-depth studies, especially in view of the much-discrepant results reported to date.[1,3,5,6,18,20] One of the key prostanoids is PGD_2. This major product of arachidonic acid, originating from mast cells, is rapidly metabolized into several compounds, out of which the stable urinary 9α,11β-PGF_2 was usually most frequently studied.

In our study, the differences of the baseline urinary 9α,11β-PGF_2 levels before placebo and aspirin challenge in the BNR versus NR group were statistically insignificant, which remains very much in line with other reports.[5,6,20] We did not detect any increase of urinary 9α,11β-PGF_2 after the oral aspirin challenge. Other authors reported the elevated postchallenge levels of this metabolite, although the encountered discrepancies might be attributable to a different aspirin challenge route.[5,6] In our recent study, no statistically significant differences in urinary 9α,11β-PGF_2 after the oral aspirin challenge were observed between the aspirin-sensitive and aspirin-tolerant asthmatic patients.[20]

The same highly accurate and sensitive method for measuring 9α,11β-PGF_2 was used in our study as the one previously applied by Bochenek et al.[20] In the above-cited reports,[5,6] the enzyme-immunoassay method was applied, making the actual comparison of the results nonviable.

Another reason why 9α,11β-PGF_2 measurements in the urine yield ambiguous data might be attributable to the fact that it is not the only PGD_2 metabolite encountered in urine. Direct serum 9α,11β-PGF_2 examination is therefore hypothesized to be a more precise marker of the mast cell activation, although the reports on it are still rather scarce.[13,20]

In our study, the mean baseline serum 9α,11β-PGF_2 levels were found to be higher in the BNR group. After aspirin challenge, a significant increase of this metabolite occurred in this group only. This is the first time that patients showing both bronchial and nasal responses to aspirin challenge were found to be characterized by higher baseline and postchallenge levels of the mean serum 9α,11β-PGF_2, as compared with the ones encountered in patients with the isolated nasal responses. The more severe course of asthma and rhinosinusitis in the BNR group might account for the higher serum baseline levels of 9α,11β-PGF_2.

The higher frequency of positive skin test results to common aeroallergens in the patients with NR to aspirin might perhaps be attributable to the fact that those patients were younger than the ones with BNR. Interestingly, the results of the large epidemiologic study on AIAR in Europe disclosed that rhinitis and asthma appeared significantly earlier in patients with positive skin test results

compared with those with the negative results.[7]

In our study, a relatively high ratio of nasal versus both nasal and bronchial responses to aspirin was observed. The data reported in this study give sufficient grounds to support a recommendation that a comprehensive diagnosis of aspirin hypersensitivity should always include careful assessment of nasal symptoms. Pleskow et al[9] found that 3 of 36 aspirin responders showed pure nasal responses. In a large group of 163 patients with aspirin hypersensitivity history, the aspirin challenge induced naso-ocular reaction in 19% of subjects.[21]

Aspirin-induced asthma/rhinitis might not be a homogenous disease. The subset of patients with reaction to aspirin restricted to the upper respiratory tract was characterized by milder and shorter-lasting disease. Furthermore, the type of specific response to aspirin challenge (ie, symptoms encountered in the lower or upper respiratory tract) appeared to be evidenced not only by the basal and postchallenge urinary LTE_4 excretion but also by serum 9α,11β-PGF_2 levels, the latter one being in fact our original finding. Any further studies into PGD_2 significance in AIAR should therefore reasonably consider the assessment of serum 9α,11β-PGF_2 as a viable and accurate method of examination.

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